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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/989,620	Applicant(s) SERIZAWA ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3, 4, 13, 14, 17, 18, 27, 28, 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,13,14,17,27,28,44,45,47 and 48* is/are rejected.

7)☐ Claim(s) *4,18 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Currently, claims 1, 3, 4, 13, 14, 17, 18, 27, 28, and 44-48 are pending in the application. Claims 1-43 were pending, and rejected in the prior action, mailed on March 26, 2003. In the Response to this action, the Applicant cancelled claims 2, 5-12, 15, 16, 19-26, and 29-43; amended claims 1, 14, 17, 18, 27, and 28; and added new claims 45-48.

2. Because this action raises issues not raised in a prior action, the action is being made Non-Final.

Information Disclosure Statement

3. It was indicated in the prior action that the following references we submitted in a foreign language accompanied by an English abstract. Due to this, the references were been examined only to the extent of the disclosure in the abstract.

Nakayama et al., Mebio, 12(10): 79-86.

Aono et al, 38th Japan Rheumatic Society Summary Collection, (1994), p. 487.

Serizawa, Saishin-igaku 54(4):917-924.

Fujisawa, Molecular Medicine 33:1254-1261.

In the response to that action, the Applicant has resubmitted these references with an English translation. In view of this, it is noted that these references have now been considered to the extent of the English translations submitted on June 23, 2003.

4. In the prior action, it was indicated that the reference JP 5-503281 in the IDS of paper 5 is in a foreign language and has none of a translation, an explanation of its relevance, or an English abstract. In response to this note, the Applicant noted that the specification on pages 1-2 provided a brief statement of the contents of this reference. In view of this, the reference will be considered to the extent that the reference is described therein. It is suggested however, for future purposes, that the Applicant note in the IDS itself the location of such concise statements in the specification as suggested in MPEP § 609 III A (3).

It is also noted that the Applicant indicated that the reference is a related family member of the reference WO 91/10448. However, no indication is provided as to the relationship and what differences or similarities may be present in the teachings of the references (no statement re: cumulative teachings in the IDS). Thus, while the WO reference has been considered, this does not provide an indication in this case as to the consideration of the JP document.

In view of the above, the Examiner has attached a copy of the IDS page citing the JP document, with the reference initialed by the Examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **(Prior Rejection- Withdrawn)** Claims 1-8, 14-22, 27, 30-37, and 42 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 14 were treated as representative of the rejected claims. These claims were rejected for two reasons. First, the applicant has not provided any guidance towards any compounds other than those listed, for example, in claim 5 that may have a synergistic effect when combined with the apoptosis-inducing antibody. Second, the applicant has not shown that any of the identified compounds other than methotrexate has such an effect. In view of the Amendments to the claims limiting the claimed embodiments to those comprising the antibodies CH11, HFE7A, and humanized antibodies thereof, and the arguments pursuant thereto, this rejection is hereby withdrawn.

7. **(Prior Rejection- Withdrawn)** Claims 1-8, 14-22, 27, 30-37, and 42 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions, and methods of treating rheumatoid arthritis using the composition, comprising an anti-human Fas antibody and methotrexate, does not reasonably provide enablement for compositions or methods wherein the composition comprises the claimed antibody and any "compound having a folate antagonistic or dihydrofolate reductase inhibiting activity." In view of the amendments to the claims limiting them to embodiments wherein the compound is methotrexate, the rejection is withdrawn.

8. **(Prior Rejection- Withdrawn)** Claims 1-43 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making and using a synergistic composition of methotrexate and the two identified antibodies,

does not reasonably provide enablement for such compositions with any anti-Fas antibody. In view of the amendment of the claims to restrict the them to embodiments wherein the antibodies are the antibodies CH11, HEF7A, or humanized forms thereof, the rejection is withdrawn.

9. **(Prior Rejection- Withdrawn)** Claims 14-29 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on methods of preventing or treating a disease comprising administering to a mammal the claimed composition. The diseases for which the claims may be used were described as "preventable or treatable by an agent having apoptosis inducing activity." The claims have been amended to recite a specific set of diseases that may be treated according to the claimed method. In view of the amendment, the rejection is withdrawn.

10. **(Prior Rejection- Withdrawn)** Claims 1-3, 6-7, 9-11, 13-17, 19-21, 23-25, 27-32, 34-36, 38-40, 42, and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods compositions, and methods of treating rheumatoid arthritis using compositions, of methotrexate and an anti-Fas antibody, does not reasonably provide enablement for the compositions and methods wherein the antibody is CHII. The claims were rejected because it was not clear that the CHII antibody was readily available to the public. In view of the Examiner's comments, the rejection is hereby withdrawn.

11. **(Prior Rejection- Withdrawn)** Claims 14-43 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating rheumatoid arthritis by administering to a human a composition comprising an anti-human Fas antibody and an compound have a folate antagonistic or a dihydrofolate reductase inhibiting activity, does not reasonably provide enablement for methods of treating or preventing any autoimmune disease or rheumatoid arthritis in any mammal using the claimed compositions. The claims were rejected for three reasons stated in the prior action as follows:

> First, the applicant has not enabled the claimed method to the extent that it reads on method of preventing the identified diseases. Second, the applicant has not shown that the claimed method would be effective in treating any autoimmune disease. Third, the applicant has not shown that a composition comprising an anti-human Fas antibody would be effective in inducing apoptosis in any mammal.

In view of the amendments to the claims, and the indications in the art that the claimed therapy for the treatment of the identified disease is a potential therapy for such autoimmune disorders, the rejection is withdrawn.

12. **(Prior Rejection- Withdrawn)** Claims 2-4, 6-8, 10-13, 16-18, 20-22, 24-26, 28, 29, 31-33, 35-37, 39-41, and 43 were rejected for lack of enablement because these claims require the use of a specific antibody. The antibodies CH11 and HFE7A are required to practice the claimed invention described by these claims. In the Response, the Applicant pointed out that the CH11 antibody is publicly available, and submitted a declaration indicating that the hybridoma cell HFE7A have been deposited under the terms of the Budapest treaty, and that any restriction s on public access to the cells will be removed upon issuance of a patent on the present application. The rejection is therefore withdrawn.

Claim Rejections - 35 USC § 102

13. **(Prior Rejection- Withdrawn)** Claims 1, 5, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Mizutani et al., Cancer, 79(6): 1180-89. As indicated above, claims 5 and 9 have been cancelled. Further, claim 1 has been amended to read on compositions comprising an anti-Fas antibody and methotrexate, wherein the antibody is one the HEF7A or CH11 antibodies, or a humanized form of either of the two identified antibodies. As neither of these antibodies has been disclosed by the reference, the rejection is withdrawn.

14. **(Prior Rejection- Withdrawn)** Claims 1, 5, and 9 were rejected under 35 U.S.C. 102(a) as being anticipated by Mizutani et al., J. Urology 160:561-570. The claims as amended have been described above. In view of the amendments to the claims such that the currently pending composition claims are limited to embodiments with one of the two identified antibodies (or humanized antibodies thereof), the rejection is withdrawn.

15. **(Prior Rejection- Withdrawn)** Claims 1, 5, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by McGahon et al, British Journal of Haematology 101:539-47. The claims as amended have been described above. In view of the claim amendments limiting the claimed invention to the two disclosed antibodies, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. **(New Rejection)** Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGahon et al, British Journal of Haematology 101:539-47, in view of Ramer et al., U.S. Patent 6,001,962. These claims read on compositions comprising a combination of the anti-Fas antibody CH11, and methotrexate. As indicated in the prior action, McGahon teaches a composition of anti-Fas antibody and methotrexate wherein the combination lead to a synergy of the apoptotic effects of the compounds. Pages 542 and 546, and Figure 7. Further, the reference also teaches that anti-Fas IgM antibodies appear to have synergistic effects with other cytotoxic drugs, including the drug methotrexate. Page 542, paragraph spanning pages 542 and 546, and page 545, figure 7. Thus, the reference suggests the combination of any anti-Fas IgM with methotrexate for therapies involving the induction of apoptosis. However, the reference does not teach the use of the antibody CH11.

Ramer teaches that the CH11 antibody is an anti-Fas IgM. Column 2, lines 54-57. Thus, it would have been obvious to one of ordinary skill in the art to have combined CH11 with methotrexate to induce cell apoptosis. Further, in view of the teachings of McGahon, one of ordinary skill in the art would also have had a reasonable expectation that such a combination would result in a synergistic effect on the efficacy of the drug combination. Thus, the references render the identified claims obvious.

18. **(New Rejection)** Claims 1, 3, 13, 14, 17, 27, 28, 44, 45, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGahon and Ramer as applied to claims 1 and 3 above, and further in view of the teachings of Genestier et al. (J Clin Invest 102(2): 322-28) and

Fujisawa et al., (J Clin Invest 98(2): 271-78- of record in the IDS of Jan. 29, 2002). The claims read on the compositions described above, and methods of treating certain diseases, including rheumatoid arthritis (RA) with the compositions.

The teachings of McGahon and Ramer have been described above. Fujisawa and Genestier teach, respectively, the utility of anti-Fas antibody, and methotrexate, in the treatment of rheumatoid arthritis. It is noted that although Fujisawa only discloses the treatment of a murine model of RA, the teachings of the reference are further supported by Firestein et al. (U.S. Patent 6,004,942, cols 1-2 - teaching the induction of apoptosis as a therapy for RA), and Serizawa et al. (EP 0866131, teaching the utility of anti-Fas antibody to treat RA). Thus, the teachings of these references indicate that both methotrexate and anti-Fas antibody are both useful in the treatment of RA. The teachings of McGahon and Ramer indicate that the two drugs are both also useful, and result in a synergistic effect when combined, for treating other disorders involving the cytotoxic/apoptosis inducing activity of the drugs. It would therefore have been obvious to those in the art to treat RA using the drug combination. Further, those in the art would have has a reasonable expectation of success not only in the use of the combination, but also of gaining the benefit of the synergism known form the combination of methotrexate and anti-Fas IgM.

Conclusion

19. No claims are allowed. Claims 4, 18, and 46 are objected to a depending on rejected claims.

20. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant it is not used as a basis for rejection for the stated reasons.

Serizawa et al., Saishin-Igaku 54(4): 917-24 (English translation submitted by the Applicant of IDS reference). This reference indicates that the anti-Fas antibody is a IgG antibody, and therefore, according to the teachings of the art (see e.g., McGahon, supra), one of ordinary skill in the art would not have expected a synergistic effect from the combination of this antibody with methotrexate. Thus, this reference is not being applied in an obviousness rejection against the claims.

Yonehara et al., Cytokine and Growth Factor Reviews 13: 393-402. This reference teaches that each of the suppression and induction of Fas-induced apoptosis can both achieve amelioration and aggravation of autoimmune disorders. Page 393. This is because Fas-induced apoptosis can lead to both positive and negative effects in these therapies. However, the reference also indicates that the anti-Fas antibody HFE7A appears to suppress the negative effects of Fas-induced apoptosis, while at the same time acting as an agonist for positive (autoimmune cell deletion) Fas activity.

Chu et al., U.S. Patent 6,544,523 (teaching the use of Fas agonists to treat autoimmune disorders, cols 10-11.)

Signore et al., Diabetes Metab Rev 14 : 197-206 (1998);
Rose et al., Brit J Rheumatol, 36: 158-63 (1997) ;
Defranco et al., Diabetes 50 : 483-88 (2001) ;
Moulian et al., Blood 89: 3287-95 (1997);
Eguchi, Int Med, 40: 275-84 (2001); and
Yonehara, Cytokine and Growth Factor Reviews, 13: 393-402 (2002).
These references are cited as either indicating that certain apoptosis inducing compositions are effective for the treatment of certain autoimmune diseases, for discussing the interrelationship between apoptosis and autoimmune disorders (and indicating that inducers of apoptosis may result in either the aggravation or amelioration of such disorders- esp. Yonehara, Intern Rev Immunol page 331).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 9/22/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600